

Covid-19: Time for a paradigm change

As of May 11, 2020, coronavirus disease 2019 (Covid-19) has been confirmed in 4 152 670 people worldwide, carrying a mortality of approximately 6.8%,¹ compared with a mortality rate of less than 1% from influenza. There is an urgent need for effective treatment. Current focus has been on the development of novel therapeutics, including antivirals as well as vaccines to provide primary protection. Accumulating evidence suggests that a subgroup of patients with severe Covid-19 might have a cytokine storm syndrome. We recommend identification and treatment of such hyper inflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality.

In order to change the approach to patients with severe general conditions by physicians (including anesthesiologists, emergency room resuscitators, infectious disease doctors, cardiologists), a few concepts must be elaborated. The conventional treatment of patients with viral infection has been antipyretic and analgesics to treat the flu-like symptoms and the use of antivirals, in those specific infections where specific antivirals have been identified. Virologists and pharmacologists succeeded in the development of antivirals mainly for herpesviruses² and HIV-1, and more recently for HBV and HCV.³ Acute viral infections, including seasonal influenza and measles, commonly resolve without treatment, although 1% to 2% of the cases may progress to severe respiratory and cardiac distress. So far, intubation and mechanical respiratory support have been available for acute respiratory distress syndrome (ARDS) patients waiting for a spontaneous recovery. Only for those with severe deterioration with no signs of improvement and often in the septic shock phase, were corticosteroids used as a last resort. But steroid efficacy is not consistent, ranging from highly effective⁴ to a negative treatment, contributing to patient mortality,⁵ so steroids are not recommended routinely for Covid-19 cases.

A new era is emerging: patient treatment with drugs specifically targeted to precise biomolecular pathways. The cytokine storm-related pneumonia observed in cancer patients treated with novel biotherapies (including CAR-T cells) has opened the field to anti-IL6R monoclonal antibodies (mAb)⁶ and other molecules that act on the IL-6/IL-6R axis.⁷ Cytokine storms have been reported also for acute syndrome associated to DNA viruses, in particular HHV-8 or EBV virus-associated hemophagocytic syndrome (VAHS).⁸ In particular, the lung injury present in Covid-19 represents a cytokine-storm reaction akin to anaphylaxis that progresses to ARDS. We propose that clinicians in the front line coping with Covid-19 should focus on this reaction and give it the urgency they would afford to traditional cases of anaphylaxis.

Physicians are more familiar with IgE-mediated anaphylaxis, which represents the major mechanism underlying allergic anaphylaxis

and is primarily mediated by histamine release (Figure 1).⁹ The **cytokine-release reaction**, mainly related to IL6 (besides TNF- α and IL-1 β), represents a hypersensitivity reaction (HSR), triggered by chimeric, humanized, and human mAbs and chemotherapeutic agents, including oxaliplatin. HSR mediators (ie, IL-6) activate monocytes, macrophages, mast cells, and other immune cells with the Fc gamma receptor (Fc γ R)—an essential player of many immune system effector functions, including the release of inflammatory mediators and antibody-dependent cellular cytotoxicity.⁹ **Cytokine storm reactions** are further characterized by activation of direct and indirect activation of the coagulation pathway. In particular the complement cascade generates anaphylatoxins, such as C3a and C5a, which bind to complement receptors resulting in the release of histamine, leukotrienes, and prostaglandins.⁹ All such molecules contribute to the main symptoms such as flushing, hives, hypoxia, vasodilation, and hypotension. In patients infected with influenza A virus (eg, H5N1), the inflammatory cytokines such as IL-1 β , IL-8, and IL-6 play a major role in mediating and amplifying **acute lung injury** (ALI) and ARDS by stimulating C5a chemotaxis. The C5a induces innate immune cells including mast cells, neutrophils, and monocytes/macrophages to release proinflammatory cytokines such as IL-12, TNF- α , and macrophage inflammatory proteins-1 α . In addition, C5a also stimulates adaptive immune cells such as T and B cells to release cytokines such as TNF- α , IL-1 β , IL-6, and IL-8. The clinical condition caused by many cytokines triggered by highly pathogenic viruses like H5N1, has been called a “cytokine storm”. Cytokines were rapidly induced at 24 hours post-infection with H5N1. The proinflammatory cytokines including IL-1 β and TNF- α might contribute to the severity of disease by promoting maximal lung inflammation caused by H5N1 viral infection.¹⁰ Cytokines have been also blamed for enhancing or modifying virus receptor exposure on endothelial cells lining the myocardial tissue, increasing susceptibility to H1N1 virus infection.¹¹ Compared to healthy volunteers, H7N9-infected patients have significantly higher levels of cytokines such as IL-6, IFN- γ -inducible protein 10 (IP-10), IL-10, IFN- γ , and TNF- α . A dangerous cytokine storm also occurs in SARS.¹⁰ The representative SARS-CoV ssRNAs had powerful immunostimulatory activities inducing releasing proinflammatory cytokines TNF- α , IL-6, and IL-12. Elevated levels of some pro-inflammatory cytokines including monocyte chemoattractant protein-1 (MCP-1), transforming growth factor-beta1 (TGF- β 1), TNF- α , IL-1, and IL-6, produced by cells infected by SARS-CoV, might cause ALI. In addition, one cytokine could induce other cytokines to further enhance the pro-inflammatory response as was noted when elevated levels of TNF- α induced other cytokines like IL-6. Thus, the cytokine storm reaction plays an important role in ALI. Limited data are available on the interaction between IL-6 and C5a. In a

Pathways of anaphylaxis

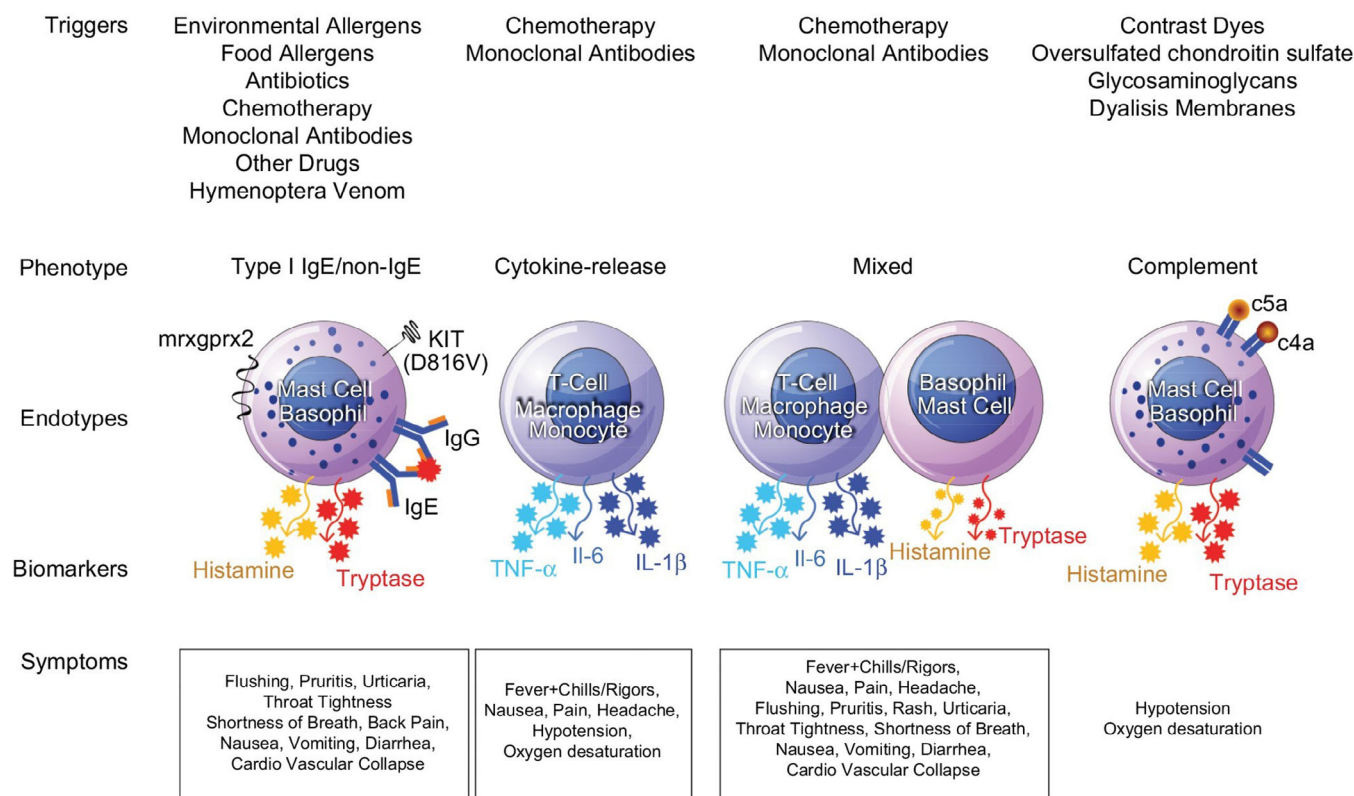


FIGURE 1 Types of anaphylaxis and the involved molecular pathways. Figure modified from Jimenez-Rodriguez TW, Garcia-Neuer M, Alenazy LA, Castells M. Anaphylaxis in the 21st century: phenotypes, endotypes, and biomarkers. *J Asthma Allergy*. 2018;11:121-142. Published 2018 Jun 20. doi: 10.2147/JAA.S159411

mouse sepsis model, IL-6 inhibition reduced the expression of tissue C5aR.¹² More recently, studies of coronary artery disease (CAD) found that IL-6 and complement may both contribute to the progression of cardiovascular diseases. In patients with non-ST-elevation myocardial infarction (NSTEMI), IL-6 inhibition with the anti-IL-6R mAb (tocilizumab) reduced C5aR1 and C5aR2 in whole blood along with decrease of C-reactive protein (CRP) and percutaneous coronary intervention (PCI)-related troponin T (TnT) release.¹³

In 2015, the authors of an article titled "The role of C5a in acute lung injury induced by highly pathogenic viral infections",¹⁰ were advocating the development of "a humanized anti-human C5a antibody would be a potential therapeutic target for highly pathogenic viral infection-induced acute lung injury". Although an anti-C5aR mAb is still in development (ie, the IPH5401 mAb, by Innate Pharma, Marseille, France),¹⁴ given the available literature on the direct correlation between reduction of C5aR1/C5aR2 and IL6-IL6R axis, it seems critical to use the available anti IL6R mAb. In particular, those formulations which have been already approved for clinical use with a different FDA/EMA indication could be subjected to smart repurposing. Many patients around the world may benefit if the scientific community maximizes the use of currently available and potentially life-saving drugs when used as effective anti-ARDS agents that also reduce cardiac stress that is present in the ongoing Covid-19 epidemic.¹⁵ This

approach would include forming a virtual global team that include those with therapeutics experience administering mAbs to patients to reduce/interrupt cytokine storm (primarily oncologists) with clinicians on the front lines of Covid-19 care (including intensivists, infectious diseases, and emergency physicians). Key research to be conducted during this pandemic should include controlled clinical trials of new mAbs and investigations of biomarkers that may have predictive value and guide the use of mAbs (like tocilizumab) to optimize selection of patients, monitor treatment, and enhance patient outcomes.

CLINICAL SYNDROMES

ALI - ACUTE LUNG INJURY

ARDS - Acute Respiratory Distress Syndrome

CAD - Coronary Artery Disease

HSR - HyperSensitivity Reaction

NSTEMI - non-ST-Elevation Myocardial Infarction

VAHS - Virus-Associated Hemophagocytic Syndrome

CYTOKINE AND CHEMOKINE LIST

IL-1 - INTERLEUKIN-1

IL-1β - Interleukin 1 beta (leukocytic pyrogen)

IL-6 - Interleukin 6

IL-6R - Interleukin 6 Receptor
 IL-8 - Interleukin 8 (or chemokine [C-X-C motif] ligand 8, CXCL8)
 IL-10 - Interleukin 10 (or human cytokine synthesis inhibitory factor -CSIF)
 IL-12 - Interleukin 12
 IFN- γ - Interferon gamma
 IP-10 - Interferon gamma inducible protein 10 kD (or CXCL10)
 TNF- α - Tumor necrosis factor- α
 TGF- β 1 - Transforming growth factor beta 1
 MIP-1 α - Macrophage inflammatory protein 1 α (CCL3)
 MCP-1 - Monocyte chemoattractant protein-1 (CCL2)

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VIRUS LIST

EBV - EPSTEIN-BARR VIRUS

H1N1 - Influenza A virus subtype H1N1 (1918 and 2009 flu pandemic)

H5N1 - Influenza A virus subtype H5N1 (Avian)

H7N9 - Influenza A virus subtype H7N9 (Avian)

HBV - Hepatitis B Virus

HCV - Hepatitis C Virus

HHV-8 - Human Herpes virus 8 (Kaposi's sarcoma-associated herpes-virus - KSHV)

HIV-1 - Human Immunodeficiency virus 1

SARS-CoV - Severe Acute Respiratory Syndrome-associated coronavirus (CoV-Urbani 2003)

SARS-CoV-2 - Severe Acute Respiratory Syndrome-associated coronavirus-2 (Cov-2019)

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OTHERS

C3A - COMPLEMENT MOLECULE C3A

C5a - Complement molecule C5a

C5aR1 - C5a Receptor 1 (or C5aR, CD88)

C5aR2 - C5a Receptor 2 (or C5L2, GPR77)

CAR-T - Chimeric antigen receptor T cells

Fc γ R - Fc gamma Receptor

EMA - European Medical Agency

FDA - U.S. Food and Drug Administration

CONFLICT OF INTEREST

The authors have no competing interest.

AUTHORS CONTRIBUTIONS

Franco M. Buonaguro: article decision, planning and writing; Paolo Ascierto: concept discussion; Luigi Buonaguro: literature search and reviewing; Maria Lina Tornesello: literature search and reviewing; Gene D. Morse: concept discussion and manuscript revision; Igor Puzanov: article discussion; Christian Br      : article reviewing; Robert C. Gallo: concept discussion and article reviewing.

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